Re: Brain and Other Central Nervous System Cancers: Recent Trends in Incidence and Mortality

The National Cancer Institute's Surveillance, Epidemiology, and End Results[1] Program has reported a 35% rise in the incidence of childhood brain cancer since 1972. Legler et al. *(1)* conclude that increased use of magnetic resonance imaging (MRI) totally accounts for this increase. I believe this claim is erroneous and inconsistent with their own evidence.

The claim that Smith et al. *(2)* persuasively linked the "rise in brain cancer incidence among children . . . to the increased availability of MRI" is open to different interpretation. That article does not examine the relationship between MRI use and the increase in brain cancer incidence. Rather, statistical modeling techniques were applied to test whether the mid-1980s increase in incidence occurred in a stepwise fashion versus a linear fashion. Smith et al. assumed, without evidence, that an environmental cause would produce a linear increase but that improvements in detection would produce a stepwise change. In fact, the stepwise model is a "straw man" that does not reflect the expected effects of any process. That analysis shows only that the rise in rates was more rapid than gradual—a conclusion that, absent more specific evidence, is compatible with essentially any cause.

Moreover, the evidence presented by Legler et al. in support of the "better detection" cause is ambiguous and can, in fact, be construed as evidence against it. If increased sensitivity for real disease had caused the increase, the incidence would have risen temporarily and then returned to baseline. The duration of the apparent increase would be approximately equal to the lead time gained by the widespread use of MRI. However, in reality, the incidence rate has not yet subsided. Therefore, under this hypothesis, we would infer that MRI has gained a lead time approaching 15 years. But Legler et al. note that 5-year survival for these children has only increased to 63% from 58% over the same period. If the survival function for these children is exponential, these findings correspond, by standard calculations *(3)*, to mean survival times of approximately 10.8 and 9.2 years, respectively. The increase in mean survival time consists of lead time and whatever real survival benefit results from early detection and from any improved efficacy of treatment during the 1980s and 1990s. Therefore, the gain in lead time is at most 1.6 years. If increased detection sensitivity accounted for the increased incidence, the return to baseline should have occurred long ago. The incidence and survival data thus conclusively exclude increased sensitivity as a cause of the increase in incidence.

Increased detection could account for a sustained increase in incidence of brain cancer, with minimal decreases in mortality only through the detection of substantial numbers of small lesions that are histologically brain cancer but would, if left alone, never surface clinically, as occurs with prostate cancer in the elderly. A typical signature of such "pseudo-disease" is the frequent incidental finding of the lesions in autopsies of people dying of unrelated causes. That phenomenon has never, to my knowledge, been reported.

The evidence presented by the authors is fully compatible with the rapid introduction and persistence of an as yet unidentified neurocarcinogen into the environment. This hypothesis has high *a priori* plausibility. In 1984, the National Academy of Sciences *(4)* reported that 15 000 of the 75 000 chemicals registered for commercial use with the U.S. Environmental Protection Agency had moderate to high potential for human exposure. Less than one half of them had been tested for toxicity at all, and fewer than 20% had been tested for toxicity in developing organisms. It would be tragic to delay investigating this type of etiology on the basis of reasoning that is viable only if there is a high prevalence of an unattested indolent form of brain cancer.

CLYDE B. SCHECHTER

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Editor's note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifies to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

Correspondence to: Clyde B. Schechter, M.D., Mount Sinai Medical Center, Department of Community and Preventive Medicine, One Gustave L. Levy Place, New York, NY 10029-6574.

RESPONSE

We appreciate the opportunity to respond to Dr. Schechter's concerns. His letter focuses exclusively on childhood brain cancer, although our article addresses trends for all ages *(1)*. Singling out childhood brain cancer overlooks our observation that changes in brain cancer incidence during the period from 1975 to 1995 coincided with changes in diagnostic practice across all ages. We refer the reader to our article for more detail concerning adult brain cancer, and below we address the specific issues raised by Dr. Schechter.

Contrary to Dr. Schechter's letter, we offered several possible explanations for the increase in incidence of childhood brain cancer that occurred during the mid-1980s *(1,2)*. There was an increased capability to detect brain cancers, particularly low-grade gliomas, as a result of diagnostic application of magnetic resonance imaging (MRI). In addition, changes in histologic classification of brain tumors occurred in the years around 1984 and 1985, and changes in neurosurgical practices occurred (e.g., stereotactic biopsies) in the mid-1980s. These changes may have led to increased diagnosis and reporting of childhood brain tumors. Our analysis does not rule out the possibility of a true in-

crease. However, the childhood brain tumor increase in the mid-1980s resulted almost exclusively from an increase in low-grade gliomas, which are preferentially detected by MRI, rather than from an increase in high-grade gliomas or medulloblastoma/primitive neuroectodermal tumor, which are easily detected by computerized tomography (CT) imaging *(3)*. The absence of a sudden increase in brain cancer mortality following the increase in incidence along with a lack of marked treatment advances strongly support the plausibility of our explanations.

Dr. Schechter doubts that the trend patterns could reflect new ascertainment of small, slow-growing lesions that are histologically malignant but never surface clinically as brain tumors. However, there are several entities that meet these criteria. In the pre-MRI era, late-onset aqueductal stenosis was of unknown causation, but it is now recognized to result from low-grade glioma arising in the tectal mid-brain region *(4)*. In addition, patients with cerebral low-grade gliomas may also present with chronic seizures *(5)*. MRI is superior to CT imaging in detecting these low-grade tumors, as evidenced by a recent report of 300 consecutive adults and children who presented with unexplained seizures *(6)*. Seventeen of these patients were found to have central nervous system tumors using MRI, but CT scans detected the tumors in less than one half of patients tested.

The Surveillance, Epidemiology, and End Results Program data for 1996 continue to confirm that childhood brain cancer rates have remained stable in the United States since the mid-1980s. Nonetheless, brain cancer trends should continue to be monitored, and analytic studies should be conducted to identify the causes of these malignancies.

JULIE M. LEGLER
LYNN A. GLOECKLER RIES
MALCOLM A. SMITH
JOAN L. WARREN
ELLEN F. HEINEMAN
RICHARD S. KAPLAN
MARTHA S. LINET

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Affiliations of authors: J. M. Legler, L. A. Gloeckler Ries, J. L. Warren (Cancer Surveillance Research Program, Division of Cancer Control and Population Sciences), M. A. Smith, R. S. Kaplan (Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis), E. F. Heineman, M. S. Linet (Division of Cancer Etiology), National Cancer Institute, Bethesda, MD.

Correspondence to: Julie M. Legler, Sc.D., National Institutes of Health, Executive Plaza North, Suite 313, Bethesda, MD 20892-7344.